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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,340	01/11/2006	Stephen James Brocchini	POLYT 9381 WO US	9022

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EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	PAPER NUMBER
1654	
MAIL DATE	DELIVERY MODE
09/23/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,340	BROCCHINI ET AL.	
	Examiner	Art Unit	
	Christina Marchetti Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-36* is/are pending in the application.

4a) Of the above claim(s) *15-26 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/17/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group IV, claims 27-35, in the reply filed on 06/03/2008 is acknowledged. The traversal is on the ground(s) that Groups I-V relate to a single inventive concept and that the reference relied upon in the previous Office action to break unity fails to teach compounds of formula I. This is not found persuasive because Wilbur *et al.* teaches a compound of formula I in Figure 2. The structure corresponds to formula I as follows: z^1 and z^2 are Fab', which are groups derived from a biological molecule linked to the rest of the structure by the nucleophilic group S from cysteine side chains; A is CH_2; B is a bond; Q-X' is bond-H; W is a carbonyl; Q is phenyl; and X is the rest of the molecule depicted in 5a, a derivatized and functionalized polymer. The specification does not limit the definition of derivatized and functionalized polymer. Broadest reasonable interpretation of this claim term encompasses $NH_2CH_2CH_2Ph$ group which is a derivatized form of polyethylene glycol.

2. The requirement is still deemed proper and is therefore made FINAL. Claims 15-36 are pending; claims 15-26 and 36 are withdrawn for pertaining to a non-elected invention.

Claim Rejections - 35 USC § 101/112

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 35 is rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility. Claim 35 is drawn to pharmaceutical composition comprising compounds of formula I. Neither the claims or the specification recite a single specific disease or condition that can be treated with the compounds of formula I. A general statement of therapeutic utility, such as treating an unspecified disease, is insufficient to establish a specific utility. Furthermore, a composition for treating an unspecified disease or condition lacks a substantial utility because it requires carrying out further research to identify or reasonably confirm a "real world" context of use.

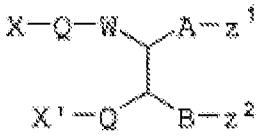
6. Claim 35 is also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

7. Claims 15-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include: 1) the scope of the invention; 2) actual reduction to practice; 3) disclosure of drawings or structural chemical formulas; 4) relevant identifying characteristics including complete structure, partial structure, physical and/or chemical properties, and structure/function

correlation; 5) method of making the claimed compounds; 6) level of skill and knowledge in the art; and 7) predictability in the art.

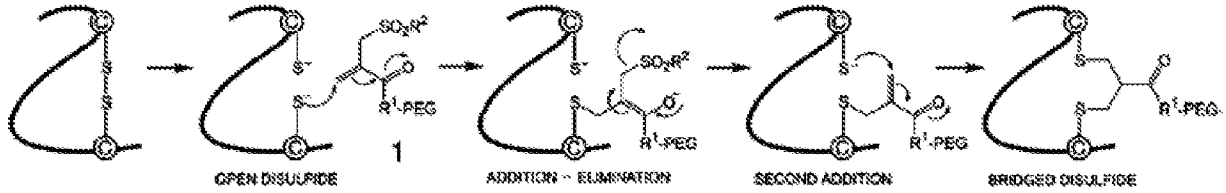
8. The claims are drawn to compounds of formula I:



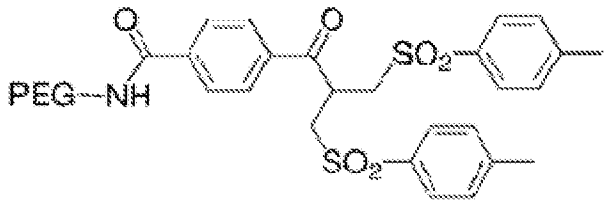
The scope of this claimed genus is indefinite owing to the use of the claim terms "derivatized or functionalized" to describe X and X', "moiety preparable by reduction of an electron-withdrawing group" to W, and "group derived from a biological molecule" to describe Z^1 and Z^2, each of which are undefined in the specification (see rejection under 35 U.S.C. 112, second paragraph below). The specification fails to adequately describe compounds of formula I that are representative of the full scope of the claimed genus. The limitations regarding Z^1 and Z^2 expand the scope of the genus to virtually any chemical moiety comprising H, C, O, N, S that can be construed as having been derived from a biological molecule; the claims are not drawn or limited to a biological molecule. In contrast, the specification narrowly describes the PEGylation of one type of biological molecule: proteins with accessible disulfide bridges. With respect to formula I, only the sub-genus in which Z^1 and Z^2 are cysteines from a native, solvent accessible disulfide bridge in a single protein, X is homo- or copolymer selected from the Markush group in claim 27, X' is H, and W is an electron-withdrawing moiety is sufficiently described.

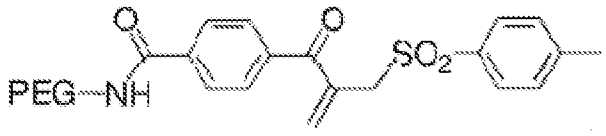
9. The specification demonstrates possession of a preferred embodiment of formula I. Specifically, the specification describes the site-specific, disulfide bridging PEGylation of an

accessible protein disulfide (p. 5, lns. 31-34, p. 10, lns 16-29, p. 11, ln. 9, p. 21, lns. 6-16, examples 4-7). This PEGylation is achieved by disulfide reduction followed by reaction with a functionalized PEG (1). The reaction involves a first thiol addition to the PEG mono-sulfone, sulfinic acid elimination to generate a second double bond and a second thiol addition. The resulting product, the protein with the bridged disulfide as depicted in the scheme below, is the preferred embodiment of formula I.



The specification discloses chemical formulas of the following PEG mono- and bis-sulfones as specific examples of PEG reagent 1:





The PEGylation reagents described in the specification have a substituted propenyl group as the conjugating moiety on the end of the PEG reagent. The conjugation moiety comprises an electron-withdrawing group (e.g. carbonyl), an α,β-unsaturated double bond, and α,β' sulfonyl group that is prone to elimination as sulfinic acid. The electron-withdrawing group is required to

promote thiol addition and to lower the pKa of the α-proton so that the elimination reaction can proceed (p. 20, lns. 16-32). This juxtaposition of the chemical functionality results in a latently cross-conjugated system.

10. The combination of the disclosure and the knowledge of one skilled in the art, puts Applicant in possession of homo- or copolymers suitable for conjugation to a protein (pp. 7-9). The specification fails to adequately describe what is meant by functionalized and derivatized. In addition, there is sufficient guidance in the specification regarding electron-withdrawing groups capable of promoting the desired reaction (p. 10, lns. 6-7). In contrast, the specification fails to adequately describe moieties preparable by reduction of an electron-withdrawing moiety that are suitable for use in the intended conjugation reaction. The specification fails to describe embodiments of formula I wherein X' is a polymer and X-Q-W is an electron withdrawing group. Finally, the specification fails to describe groups derived from biological molecules other than cysteines from a native, solvent accessible disulfide bridge in a single protein that can be conjugated by the recited PEGylation reagents.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 27-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

13. Claim 27 recites the limitation "homo- or co-polymers optionally being derivatized or functionalized". The specification fails to define the limits of derivatized and functionalized. Owing to this lack of definition, it is not clear which groups are included in the genus.

14. Claim 27 recites the limitation "a moiety preparable by reduction of an electron-withdrawing moiety". The specification fails to define the structural limits of this variable. Virtually any chemical moiety could be preparable by a method comprising a reduction of an electron-withdrawing group as there on no limits placed on additional steps that can be included in the preparation method.

15. Claim 27 recites the limitation "a group being derived from a biological molecule". The specification fails to limit the definition of this claim term. Virtually any group comprising O, N, C, H, S, P etc could be construed as being derived from a biological molecule.

Claim Rejections - 35 USC § 102

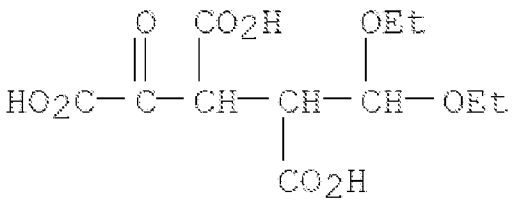
16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claim 27 is rejected under 35 U.S.C. 102(b) as being anticipated by Wilbur *et al.* (*Bioconj. Chem.*, **1994**, *5*, 220. Wilbur *et al.* teaches a compound of formula I in Figure 2. The structure corresponds to formula I as follows: z^1 and z^2 are Fab', which are groups derived from a biological molecule linked to the rest of the structure by the nucleophilic group S from cysteine side chains; A is CH_2; B is a bond; Q-X' is bond-H; W is a carbonyl; Q is phenyl; and X is the rest of the molecule depicted in 5a, a derivatized and functionalized polymer. The specification

does not limit the definition of derivatized and functionalized polymer. Broadest reasonable interpretation of this claim term encompasses $NH_2CH_2CH_2Ph$ group which is a derivatized form of polyethylene glycol.

18. Claim 27 is rejected under 35 U.S.C. 102(b) as being anticipated by Kornfield *et al.* (*J. Org. Chem.*, **1954**, *19*, 1671-80). Kornfield *et al.* teach:



wherein W is C(O)COH2, Z1 is H, which is found in biological molecules, attached to C=O (A) by the nucleophile O; Z2 is H, which is found in biological molecules, attached to C=O (B) by the nucleophile O; and X' is a derivative of polyethylene glycol.

Conclusion

19. No claims are allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571)272-9044. The examiner can normally be reached on Monday-Thursday, 9:00 A.M. to 3:00 P.M.

21. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

22. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654

/Christina Marchetti Bradley/
Examiner, Art Unit 1654